Antibacterial Agents

This invention relates to novel hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity, to methods of treatment using such compounds, and to pharmaceutical and veterinary compositions comprising such compounds.

Background to the Invention

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes, and/or which are effective against the causative organisms of community acquired respiratory infections, and/or which are selective in their pharmacological activity, thus reducing risk of unwanted side effects..

Amongst the Gram-positive pathogens, such as staphylococci, streptococci, mycobacteria and enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*

Brief Description of the Invention

This invention makes available a new class of hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity. The compounds are characterised inter alia by the presence of a hydrazide feature in their structural

backbone.

Although it may be of interest to establish the mechanism of action of the compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

Related Prior Art

Although there are many publications disclosing both hydroxamic acid and N-formyl hydroxylamine derivatives as inhibitors of various metalloenzymes such as angiotensin converting enzyme, enkephalinase and the matrix metalloproteinases, there are relatively few relating to such compounds as antibacterial agents. The following patent publications are relevant in that connection:

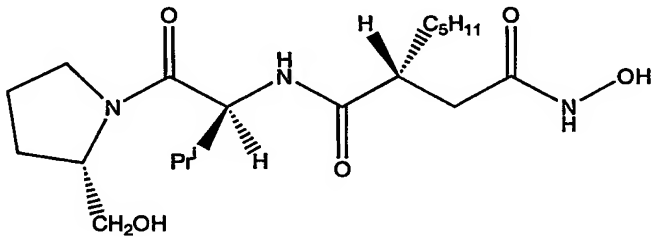
WO 99/39704 (British Biotech)
WO 99/57097 (Versicor)
WO 99/59568 (British Biotech)
WO 00/35440 (British Biotech)
WO 00/44373 (British Biotech)
WO 00/58294 (British Biotech)
WO 00/61134 (British Biotech)
WO 01/10835 (British Biotech)
WO 01/38561 (Questcor)
WO 01/40198 (Aventis)
WO 01/42431 (Bayer)
WO 01/44178 (Versicor)
WO 01/44179 (Versicor)
WO 01/85160 (SmithKline Beecham)
WO 01/85170 (SmithKline Beecham)
WO 02/28829 (Questcor)
WO 02/41886 (British Biotech)

WO 02/50081 (British Biotech)

WO 02/070541 SmithKline Beecham) relates to PDF inhibitor compounds which have a hydrazide feature in the backbone and an N-formylhydroxylamino metal binding group.

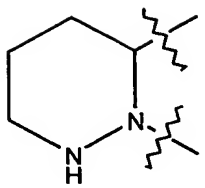
In addition the natural antibiotic actinonin (see for example J.C.S Perkin I, 1975, 819) is a hydroxamic acid derivative of Structure (A):

(A)



which is now known to act by inhibition of PDF. In addition to actinonin, various structural analogues of actinonin have also been shown to have antibacterial activity (see for example Devlin et al. Journal of the Chemical Society. Perkin Transactions 1 (9):830-841, 1975; Broughton et al. Journal of the Chemical Society. Perkin Transactions 1 (9):857-860, 1975).

The matlystatin group of compounds share a number of structural similarities with actinonin. Both are peptidic molecules with functional hydroxamic acid metal binding groups (Ogita et al., J. Antibiotics. 45(11):1723-1732; Tanzawa et al., J. Antibiotics. 45(11):1733-1737; Haruyama et al., J. Antibiotics. 47(12):1473-1480; Tamaki et al., J. Antibiotics. 47(12):1481-1492). The matlystatins and their close structural analogues are characterised by the presence in the molecule of a divalent piperazin-1, 6-diyl group, i.e.



In view of their close structural similarity to actinonin, the observation that actinonin inhibits PDF implies that matlystatin compounds may also inhibit PDF.

For a recent review of peptide deformylase inhibitors, see Clements et. al., Curr. Med. Chem. - Anti-Infective Agents, 2002, 1, 239-249.

The following patent publications disclose N-formyl hydroxylamine structures:

EP-B-0236872	(Roche)
WO 92/09563	(Glycomed)
WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)
WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)
WO 98/38179	(GlaxoWellcome)
WO 98/47863	(Labs Jaques Logeais)

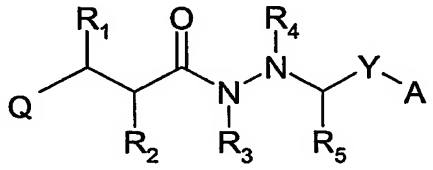
The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis.

In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives. However, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) discloses certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors.

There are too many publications relating to metalloenzyme inhibiting hydroxylamic acid derivatives to summarise effectively. However a recent review, Whittaker et. al. Chem. Rev. 1999, 99, 2735, provides an overview of that art.

Description of the invention

The present invention provides a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



(I)

wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

Y represents -C(=O)-, -C(=S)-, -S(=O)-, or $-SO_2-$;

R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula -N(OH)CH(=O), a hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkenyloxy, halogen, amino, C_1-C_6 alkylamino, or di-(C_1-C_6 alkyl)amino group

R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, C_1-C_3 alkyl-O-C_1-C_3 alkyl, C_1-C_3 alkyl-S-C_1-C_3 alkyl, cycloalkyl(C_1-C_3 alkyl)-, aryl(C_1-C_3 alkyl)-, heterocyclyl(C_1-C_3 alkyl)-, or R^1R^2N-C_1-C_3 alkyl group wherein R^1 represents hydrogen or C_1-C_3 alkyl and R^2 represents C_1-C_3 alkyl, or R^1R^2N- represents a cyclic amino group;

R_3 and R_5 independently represent hydrogen or a substituted or unsubstituted C_1-C_6 alkyl group or R_3 and R_5 taken together with the carbon and nitrogen atoms to which they are respectively attached form a saturated heterocyclic ring of from 5 to 7 ring atoms, which may be fused to a second carbocyclic or heterocyclic ring, either of which rings may optionally be substituted;

R_4 represents hydrogen or a substituted or unsubstituted C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, aryl, heterocyclyl, C_1-C_3 alkyl-O-C_1-C_3 alkyl, C_1-C_3 alkyl-S-(C_1-C_3 alkyl)-, C_1-C_3 alkyl-NH-(C_1-C_3 alkyl)-, cycloalkyl(C_1-C_3 alkyl)-, heterocyclic(C_1-C_3 alkyl)- or aryl(C_1-C_3 alkyl)- group; and

A represents a primary, secondary or tertiary amino group or a group -R_6, -OR_6, wherein R_6 is a substituted or unsubstituted C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, aryl, heterocyclyl, C_1-C_3 alkyl-O-(C_1-C_3 alkyl), C_1-C_3 alkyl-S-(C_1-C_3 alkyl), C_1-C_3 alkyl-NH-(C_1-C_3 alky)-l, cycloalkyl(C_1-C_3 alkyl)-, heterocyclic(C_1-C_3 alkyl) or aryl(C_1-C_3 alkyl)- group.

In another aspect, the invention provides a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (I) as defined above. Also included in the invention is the use of a compound of formula (I) as defined above for inhibiting bacterial growth in vitro and in vivo in mammals, and the use of such a compound for the manufacture of a composition for treating bacterial infection by inhibiting bacterial growth.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a

compound of formula (I) as defined above to the site of contamination.

The compounds of formula (I) as defined above may be used as component(s) of antibacterial cleaning or disinfecting materials.

As used herein terms of the form "(C_a-C_b)alkyl" where a and b are integers refer to a straight or branched chain alkyl moiety having from a to b carbon atoms. Thus, for example, the term "(C_1-C_6)alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein terms of the form "divalent (C_a-C_b)alkylene radical" where a and b are integers refer to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valencies.

As used herein terms of the form "(C_a-C_b)alkenyl" where a and b are integers refer to straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. Thus, for example, the term "(C_1-C_6)alkenyl" means a straight or chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond, and includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_a-C_b alkynyl" where a and b are integers refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. Thus, for example, the term "(C_1-C_6)alkynyl" would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic group, and to groups consisting of two covalently linked monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and napthyl.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring containing one or more heteroatoms. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a 5-7 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, including for example, pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzofuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy, mercapto, $(C_1$-$C_6)$alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1$-$C_6)$alkyl group.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several actual or potential chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereoconfiguration of the carbon atom carrying the R_2 group is R.

In the compounds of the invention, in relation to the groups Q, R_1, R_2, R_3, R_4, Y and A, separately and in combination:

The group Q

It is currently preferred that Q is an N-formyl hydroxylamine group -N(OH)CH(=O).

The radical -Y-

It is currently preferred that -Y- is -C(=O)- or $-SO_2-$.

The group R_1

R_1 may be, for example, hydrogen, methyl, trifuoromethyl or, in the case where Q is a hydroxamic acid group HONHCO-, fluorine. Hydrogen is currently preferred.

The group R_2

R_2 may be, for example:

optionally substituted C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl or cycloalkyl;

phenyl(C_1-C_6 alkyl)-, phenyl(C_3-C_6 alkenyl)- or phenyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl(C_1-C_6 alkyl)-, cycloalkyl(C_3-C_6 alkenyl)- or cycloalkyl(C_3-C_6 alkynyl)- optionally substituted in the cycloalkyl ring; or

$CH_3(CH_2)_pO(CH_2)_q-$ or $CH_3(CH_2)_pS(CH_2)_q-$, wherein p is 0, 1, 2 or 3 and q is 1,

2 or 3.

Specific examples of R_2 groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl, 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-acetyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at R_2 are $(C_1$-$C_6)$alkyl-, cycloalkylmethyl-, $(C_1$-$C_3)$alkyl-S-$(C_1$-$C_3)$alkyl-, or $(C_1$-$C_3)$alkyl-O-$(C_1$-$C_3)$alkyl-, especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

The group R_4

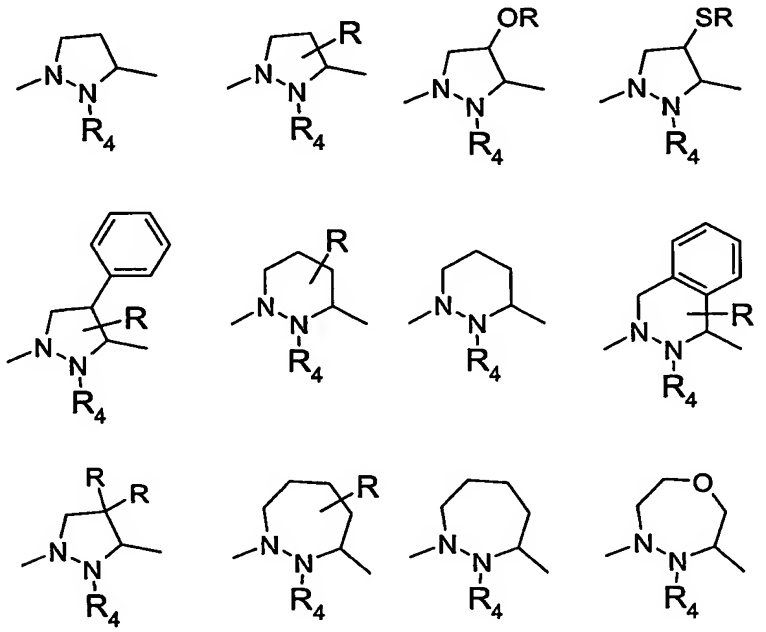
Examples of the group R_4 include hydrogen, $(C_1$-$C_6)$alkyl-, cycloalkylmethyl-, $(C_1$-$C_3)$alkyl-S-$(C_1$-$C_3)$alkyl-, or $(C_1$-$C_3)$alkyl-O-$(C_1$-$C_3)$alkyl-, especially methyl, ethyl, n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

R_3 and R_5 when not part of a ring

When not part of a ring, R_3 and R_5 may independently be, for example, hydrogen, $(C_1$-$C_6)$alkyl-, cycloalkylmethyl-, $(C_1$-$C_3)$alkyl-S-$(C_1$-$C_3)$alkyl-, or $(C_1$-$C_3)$alkyl-O-$(C_1$-$C_3)$alkyl-, especially methyl, ethyl, n- propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

The ring formed by R_3 and R_5 and the nitrogens to which they are attached

Examples of rings which may be formed by R_3 and R_5 taken together with the carbon and nitrogen atoms to which they are respectively attached are the following, wherein R_4 is as defined in relation to formula (I) and R represents hydrogen or C_1-C_4 alkyl:



In the above rings, where a sulfur atom is present as a ring member, the equivalent structures wherein that sulfur is oxidised to -SO- or -SO_2- are also examples of ring structures which may be formed by R_3 and R_5.

The group A

The group A is a primary, secondary or tertiary amino group or a group -R_6, or -OR_6. When A is -R_6, or -OR_6, the R_6 group may be, for example, any of those given as R_2 examples above, or a group of formula (II) as defined below, including such specific examples of groups (II) as morpholinyl, furanyl, thienyl, phenyl, and benzyl..

Presently it is preferred that A is a secondary or tertiary amino group, and in the

latter case it may be a non-cyclic or a cyclic amino group. For example, A may be an amino group of formula - NR_6R_7 wherein R_6 and R_7 independently represent a radical of formula (IV)

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad (IV)$$

wherein

m, p and n are independently 0 or 1;

Z represents hydrogen or a carbocyclic or heterocyclic ring of 5 to 7 ring atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms;

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, -$S(O_2)$-, -C(=O)-, -NH-, -NR_7- where R_7 is C_1-C_3 alkyl;

and wherein

Alk^1, Alk^2 and Z when other than hydrogen, independently are optionally substituted by

(C_1-C_3)alkyl, (C_2-C_3)alkenyl, or (C_2-C_3)alkynyl,

phenyl, optionally substituted by (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halo, nitro, amino, mono- or di-(C_1-C_3)alkylamino, cyano or trifluoromethyl;

monocyclic 5 or 6-membered heterocyclic, optionally substituted by (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halo, nitro, amino, mono- or di-(C_1-C_3)alkylamino, cyano or trifluoromethyl

benzyl, optionally substituted in the phenyl ring by (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halo, nitro, amino, mono- or di-(C_1-C_3)alkylamino, cyano or trifluoromethyl,

hydroxy, phenoxy, (C_1-C_6)alkoxy, or hydroxy(C_1-C_6)alkyl,

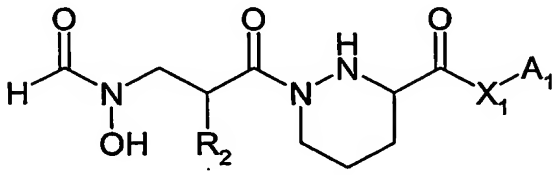
mercapto, (C_1-C_6)alkylthio or mercapto(C_1-C_6)alkyl,
oxo,
nitro,
cyano
halo
-COOH, or -$COOR^A$,
-$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$
-COR^A, -SO_2R^A,
-$NHCOR^A$,
-NH_2, -NHR^A, or -NR^AR^B,
wherein R^A and R^B are independently a (C_1-C_6) alkyl group, R^A and R^B taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by (C_1-C_3)alkyl, hydroxy, or hydroxy(C_1-C_3)alkyl.

The amino group A may also be one of formula -NR_8R_9 wherein R_8 and R_9 when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring of 5 to 8 atoms optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms, any of which rings being optionally substituted by a radical of formula (IV) as defined above. Examples of cyclic amino groups are 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, hexahydroazipino, thiomorpholino, diazepino, and thiazolidinyl. Presently preferred are piperidin-1-yl and 1-piperazinyl.

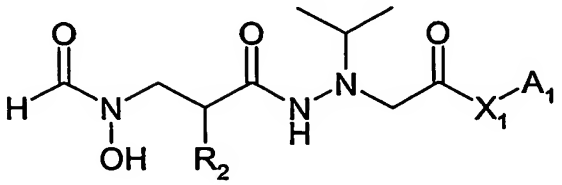
The group of formula (IV)

In the substituent (IV) Alk^1 and Alk^2 may independently represent, for example -(CH_2)- or -(CH_2CH_2)-. In the case where m is 0 and p is 1, X may be, for example -S-, -S(=O)-, or preferably -C(=O)- or -S(O_2)-. In such cases n may be 0 or 1

Compounds of the invention include those selected from the group consisting of compounds of formulae (IIA) - (IID).



(IIA)



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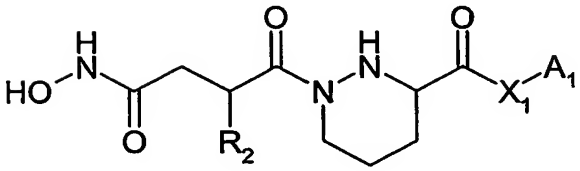

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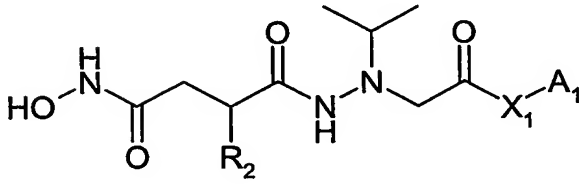


(IID)

wherein R_2 is as defined in relation to formula (IV), especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

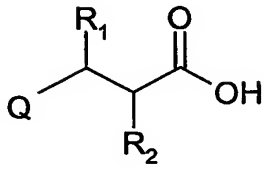
X_1 is a bond, C_1-C_3 alkylene, -NH- or -O-; and

A_1 is optionally substituted C_1-C_6 alkyl, cycloalkyl, aryl, or heterocyclic, for example methyl, ethyl phenyl, cyclopentyl, cyclohexyl, 2- or 3-furanyl, 2- or 3- thienyl, 2-, 3- or 4-pyridyl, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-oxazolyl, or 3-, 4- or 5-thiazolyl, methoxymethyl, 3,5-bis-(trifluoromethyl)phenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 3,4-methylenedioxyphenyl, 4-fluorophenyl benzyl, 3-pyridyl, 4-pyridyl, cyclohexyl, 1,3-dimethylpyrazol-5-yl, 1-methylimidazol-5-yl, and 2-[morpholin-1-yl]pyrid-5-yl.

Particular compounds of the invention include those of the Examples herein.

In general, compounds of the invention are accessible by conventional synthetic procedures. For example, they may be prepared by condensation of an acid of

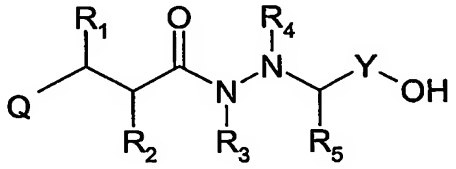
formula (IIIA) with a hydrazide of formula (IIIB):



(IIIA)

(IIIB)

In addition, compounds wherein A is a primary, secondary or tertiary amino group may be prepared by condensation of a compound of formula (III) or an activated derivative thereof with the appropriate amine:



(IIIC)

As is conventional, any reactive constituents of the intermediates used in the above reactions may be protected during the condensation reaction and deprotected subsequently.

The Examples herein provide further details of routes and methods for the preparation of compounds of the invention.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration

may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate embodiments of the invention.

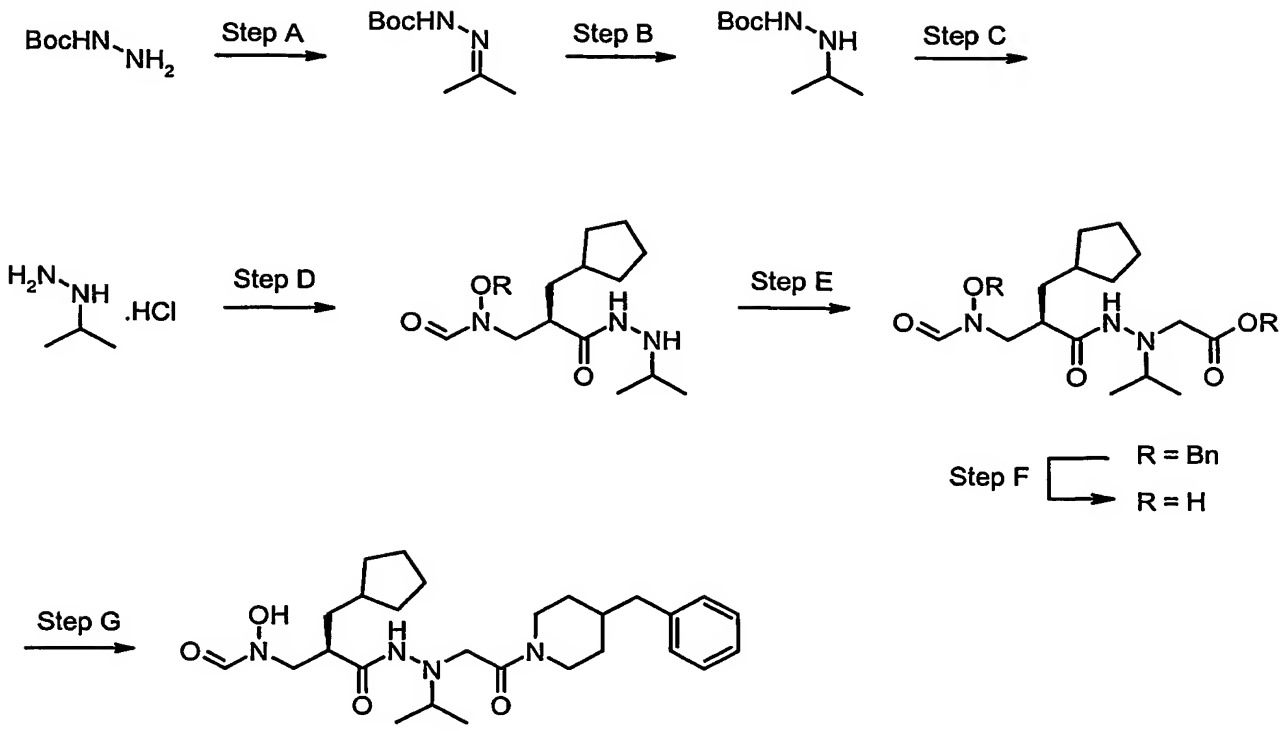
In the Examples, the following abbreviations have been used:

DMF	Dimethylformamide
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography

LRMS	Low resolution mass spectrometry
NMR	Nuclear magnetic resonance
RT	Retention Time
TLC	Thin layer chromatography
DIEA	N,N-diisopropylethylamine
DCM	Dichloromethane
HATU	O-(7-Azabenzotriazo-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 and 62.9MHz, respectively. Mass spectra were obtained using a Perkin Elmer Sciex API 165 spectrometer using both positive and negative ionisation modes. Infra-red spectra were recorded on a Perkin Elmer PE 1600 FTIR spectrometer. Analytical HPLC was performed on a Beckman System Gold, using Waters Nova Pak C18 column (150 mm, 3.9 mm) with 20 to 90 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 0.05% TFA in 10% water 90% methanol; Solvent B: 0.05% TFA in 10% methanol 90%], detection wavelength at 230 nm. Preparative HPLC was performed on a Gilson autoprep instrument using a C18 Waters delta prep-pak cartridge (15μm, 300 A, 25 mm, 10 mm) with 20 to 90 % solvent B gradient (6 ml/min) as the mobile phase. [Solvent A water; Solvent B: methanol], UV detection was at 230 nm.

Example 1



Step A: acetone, $NaBH(OAc)_3$, THF, rt, 16 h; Step B: H_2, 5% Pt/C, MeOH, 1.45 h; Step C: 4M HCl, 1,4-dioxane, rt, 2 h; Step D: 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid, HATU, collidine, DCM, 0°C, 15 min, *then* hydrazine, 0°C, 1 h; Step E: benzyl 2-bromoacetate, DIEA, CH_2Cl_2, 45°C, 16 h; Step F: H_2 (g), 10% Pd/C, MeOH, rt, 2 h; Step G: EDAC, HOAt, DCM, 0°C, 15 min, *then* 4-benzyl piperidine, 0°C to rt, 16 h.

Step A:

Isopropylidine hydrazine

To a solution of *tert*-butyl carbazate (2.64 g, 20 mmol) in THF (50 ml) at rt under argon was added acetone (1.61 ml, 22 mmol) and sodium triacetoxyborohydride (4.45 g, 22 mmol). The resulting suspension was stirred for 16 h. After this time the mixture was concentrated under reduced pressure and the crude product was partitioned between EtOAc and sat. $NaHCO_3$. The organic layer was separated, washed with sat. NaCl, dried ($MgSO_4$), filtered and concentrated under reduced

pressure to give a pale yellow oil. This oil was purified by chromatography on silica eluting with 50% EtOAc/hexanes to give the title compound as a white solid (2.95 g, 85%). 1H-NMR; δ($CDCl_3$), 7.34 (1H, s, NH), 2.04 (3H, s, CH_3), 1.81 (3H, s, CH_3), 1.51 (9H, s, $(CH_3)_3$). LRMS: +ve ion: 195 [M+23], 117.

Step B:

N'-(Isopropyl)-hydrazine carboxylic acid *tert*-butyl ester

To a solution of isopropylidine hydrazine (2.94 g, 17.1 mmol) in MeOH at rt under argon was added 5% Pt/C (290 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1.5 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure. The crude material that remained was then redissolved in EtOAc and washed with sat. $NaHCO_3$. The organic layer was separated, washed with sat. NaCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on silica eluting with 50% EtOAc/hexanes gave the title compound as colourless crystals (2.08 g, 70%). 1H-NMR; δ ($CDCl_3$), 6.34 (1H, s NHBoc), 3.50 (1H, br, NH) 3.13 (1H, sept, J=6.5Hz, $CH(CH_3)_2$), 1.46 (9H, s, $(CH_3)_3$), 1.02 (6H, d, J=6.5Hz, $(CH_3)_2CH$). LRMS: +ve ion: 197 [M+23], 175 [M+1], 161.

Step C:

Isopropyl hydrazine hydrochloride

To *N'*-(Isopropyl)-hydrazine carboxylic acid *tert*-butyl ester (1.26 g, 7.24 mmol) at rt in air was added 4M HCl in 1,4-dioxane (25 ml). The mixture was stirred for 2 h and then concentrated under reduced pressure to give a white solid which was used in the next step (assumed quantative yield, 7.24 mmol).

Step D:

N-Benzyloxy-*N*-[3-cyclopentyl-(2*R*)-(*N'*-isopropylhydrazinocarbonyl)-propyl]-formamide

To a solution of the 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid

(190 mg, 0.62 mmol) in DCM (5 ml) at 0°C under argon was added HATU (237 mg, 0.62 mmol) followed by collidine (165 µl, 2.49 mmol). The resulting mixture was stirred for 5 min at rt before the amine hydrochloride (69 mg, 0.62 mmol) was added as a solution in DCM (1 ml) and collidine (165 µl, 2.49 mmol). The reaction was stirred at 0°C for 1 h and then the mixture was concentrated under reduced pressure. The crude material was partitioned between EtOAc and sat. $NaHCO_3$. The organics were separated, washed with sat. NaCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil. This oil was purified by chromatography on silica eluting with 70-100% EtOAc/hexanes to give the title compound as a colourless oil (119 mg, 53%).1H-NMR; δ($CDCl_3$), 8.12 (0.67H, s, CHO), 7.86 (0.33H, br s, CHO), 7.5-7.3 (6H, br m, ArH and NH), 4.9-4.6 (2H, br m, OCH_2Ph), 3.8-3.6 (2H, br m, CH_2NO), 3.01 (1H, sept, J=6.5Hz, $C\underline{H}(CH_3)_2$), 2.5-2.4 (1H, m, CHCO), 1.8-1.3 (9H, m), 1.2-0.9 (2H, m), 0.98 (6H, d, J=6.5Hz, $(C\underline{H}_3)_2CH$). LRMS: +ve ion: 362 [M+1].

Step E:

{*N*'-[3-(Benzyloxy-formyl-amino)-(2*R*)-cyclopentylmethyl-propionyl]-*N*-isopropyl-hydrazino}acetic acid benzyl ester

To *N*-benzyloxy-*N*-[3-cyclopentyl-(2*R*)-(*N*'-isopropylhydrazinocarbonyl)-propyl]-formamide (69 mg, 0.191 mmol) in DCM (2.5 ml) under argon was added benzyl 2-bromoacetate (30 µl, 0.19 mmol) followed by DIEA (33 µl, 0.19 mmol). The reaction was stirred at 45°C for 16 h. After this time, methylisocyanate polystyrene resin (198 mg, 0.09 mmol)(200-400 mesh, 1.45 mmol/g) was added and the mixture shaken for 12 h. The mixture was filtered and concentrated under reduced pressure to give a crude product which was purified by chromatography on silica eluting with EtOAc to give the title compound as a colourless oil (32 mg, 33%). 1H-NMR; δ($CDCl_3$), 8.1-7.8 (1H, m, CHO), 7.6-7.2 (10H, m, 2 x Ph), 5.3-5.0 (2H, m, $NOCH_2$), 5.0-4.6 (2H, m, NCH_2CO), 3.8-3.5 (4H, m, CH_2NO and CO_2CH_2), 3.3-3.1 (1H, m, $C\underline{H}(CH_3)_2$), 3.1-2.4 (1H, br m, $COC\underline{H}CH_2$), 1.9-0.8 (11H, m), 1.04 (6H, d, J=6.5Hz, $CH(C\underline{H}_3)_2$); LRMS: +ve ion: 532 [M+23], 510 [M+1].

Step F:

{*N'*-[(2*R*)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}acetic acid

To a solution of the {*N'*-[3-(benzyloxy-formyl-amino)-(2*R*)-cyclopentylmethyl-propionyl]-*N*-isopropyl-hydrazino}acetic acid benzyl ester (31 mg, 0.061 mmol) in EtOH at rt under argon was added 10% Pd/C (5 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give a colourless oil (18 mg, 92%). 1H-NMR; δ (CD_3OD), 8.23 (0.3H, s, CHO), 7.84 (0.7H, s, CHO), 3.9-2.6 (6H, m), 1.9-0.9 (17H, m). LRMS: +ve ion: 352 [M+23], 330 [M+1].

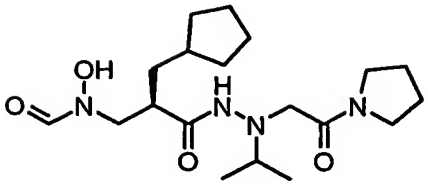
Step G:

N-(2-{*N'*-[(2*R*)-(4-Benzyl-piperidin-1-yl)-2-oxo-ethyl]-*N'*-isopropyl-hydrazinocarbonyl}-3-cyclopentyl propyl)-*N*-hydroxy formamide

To a solution of {*N'*-[(2*R*)-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}acetic acid (18 mg, 0.055 mmol) in DMF (2 ml) at 0°C under argon was added EDAC (13 mg, 0.066 mmol) and HOAt (11 mg, 0.083 mmol). The resulting mixture was stirred for 15 min before 4-benzylpiperidine (11 μl, 0.083 mmol) was added. The reaction was stirred for 15 min at 0°C and then warmed to rt where it was maintained for 16 h. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x2) and the combined organics washed with sat. NaCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil. Purification by preparative HPLC gave the title compound as a colourless oil (6 mg, 22%).1H-NMR; δ(CD_3OD), 8.23 (0.33H, s, CHO), 7.84 (0.67H, s, CHO), 7.3-7.0 (5H, m, Ph), 4.5-4.0 (2H, m, CH_2CO), 3.8-2.6 (8H, m), 2.6-2.5 (2H, m, CH_2Ph), 1.9-0.9 (22H, m). LRMS: +ve ion: 362 [M+1].

Example 2

Prepared according to Reaction Scheme 1

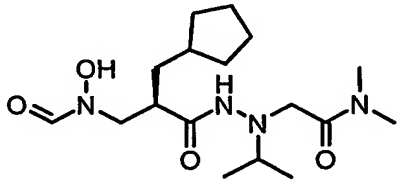


N-{3-Cyclopentyl-(2R)-[*N'*-isopropyl-*N'*-(2-oxo-2-pyrrolidin-1-yl-ethyl)-hydrazinocarbonyl]-propyl}-*N*-hydroxy-formamide

Clear colourless oil (28 mg, 48%).1H-NMR; $\delta(CD_3OD)$, 8.23 (0.4H, s, CHO), 7.84 (0.6H, s, CHO), 3.9-3.1 (9H, m), 2.9-2.6 (1H, m, $NC\underline{H}Me_2$), 2.1-1.0 (15H, m), 1.06 (6H, d, J 6.5, $CH\underline{Me_2}$). LRMS: +ve ion: 405 [M+23], 383 [M+1].

Example 3

Prepared according to Reaction Scheme 1

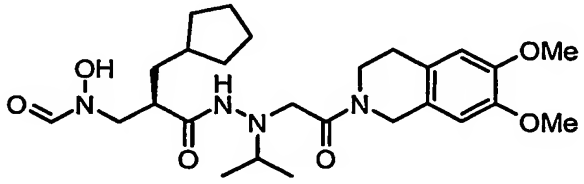


2-{*N'*-[(2R)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}-*N*,*N*-dimethyl-acetamide

Clear colourless oil (27 mg, 50%).1H-NMR; $\delta(CD_3OD)$, 8.24 (0.3H, s, CHO), 7.84 (0.7H, s, CHO), 3.8-2.4 (6H, m), 3.14 (3H, s, NMe), 2.88 (3H, s, NMe), 2.0-0.9 (17H, m). LRMS: +ve ion: 379 [M+23], 357 [M+1].

Example 4

Prepared according to Reaction Scheme 1



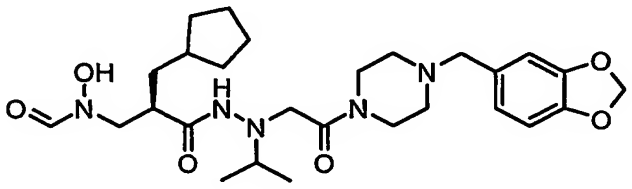
N-{3-Cyclopentyl-(2R)-[*N'*-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxo-

ethyl]-*N'*-isopropyl-hydrazinocarbonyl}-propyl)-*N*-hydroxy-formamide

Clear colourless oil (6 mg, 8%).1H-NMR; $\delta(CD_3OD)$, 8.2-7.8 (1H, m, CHO), 6.8-6.7 (2H, m, ArH), 4.8-4.4 (2H, m), 4.0-2.5 (16H, m), 1.9-1.0 (17H, m). LRMS: +ve ion: 527 [M+Na], 505 [M+1].

Example 5

Prepared according to Reaction Scheme 1

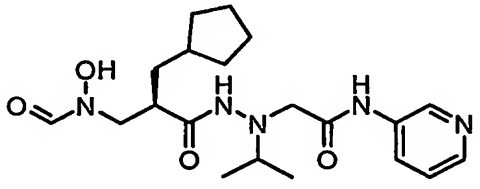


N-(2-{*N'*-[(2*R*)-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-*N'*-isopropyl-hydrazinocarbonyl}-3-cyclopentyl propyl)-*N*-hydroxy formamide

colourless oil (34 mg, 42%).1H-NMR; $\delta(CD_3OD)$, 1H-NMR; $\delta(CD_3OD)$, 8.23 (0.3H, s, CHO), 7.83 (0.7H, s, CHO), 6.9-6.7 (3H, m, ArH), 5.92 (2H, s, OCH_2O), 3.9-2.2 (16H, m), 2.0-0.9 (17H, m). LRMS: +ve ion: 332 [M+1].

Example 6

Prepared according to Reaction Scheme 1

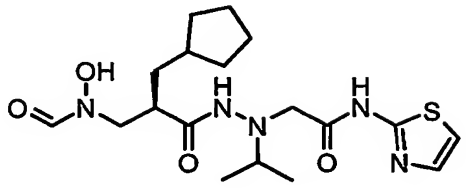


2-{*N'*-[(2R)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}-*N*-pyridin-3-yl-acetamide

colourless oil (20 mg, 32%).1H-NMR; $\delta(CD_3OD)$, 1H-NMR; $\delta(CD_3OD)$, 8.87 (1H, dd, *J* 7.5 & 2, ArH), 8.25 (1H, d, *J* 5, ArH), 8.20 (0.45H, s, CHO), 8.2-8.1 (1H, m, ArH), 7.80 (0.55H, s, CHO), 7.40 (1H, dd, *J* 8.5 &5, ArH), 3.8-3.1 (5H, m), 3.0-2.6 (1H, m, $NC\underline{H}Me_2$), 1.9-0.7 (17H, m). LRMS: +ve ion: 428 [M+23], 406 [M+1].

Example 7

Prepared according to Reaction Scheme 1

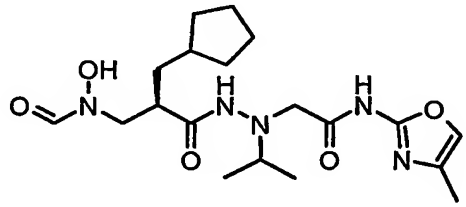


2-{*N'*-[(2R)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}-*N*-thiazol-2-yl-acetamide

colourless oil (28 mg, 44%).1H-NMR; $\delta(CD_3OD)$, 1H-NMR; $\delta(CD_3OD)$, 8.19 (0.3H, s, CHO), 7.79 (0.7H, s, CHO), 7.44 (1H, d, *J* 3.5, ArH), 7.12 (1H, d, *J* 3.5, ArH), 3.9-3.1 (5H, m), 2.9-2.5 (1H, m, NC<u>H</u>Me_2), 1.9-0.8 (17H, m). LRMS: +ve ion: 434 [M+23], 412 [M+1].

Example 8

Prepared according to Reaction Scheme 1

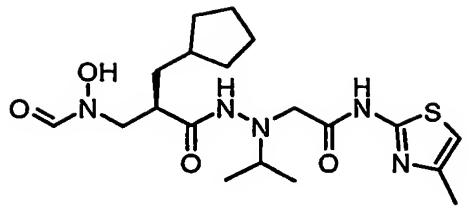


2-{*N'*-[(2R)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}-*N*-(4-methyl-oxazol-2-yl)-acetamide

colourless oil (6 mg, 10%).1H-NMR; $\delta(CD_3OD)$, 1H-NMR; $\delta(CD_3OD)$, 8.20 (0.3H, s, CHO), 7.83 (0.7H, s, CHO), 7.33 (1H, s, ArH), 3.8-3.1 (5H, m), 2.9-2.6 (1H, m, NC<u>H</u>Me_2), 2.10 (3H, s, ArMe), 2.0-1.0 (17H, m). LRMS: +ve ion: 432 [M+23], 410 [M+1].

Example 9

Prepared according to Reaction Scheme 1

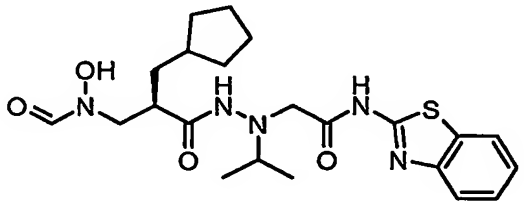


2-{*N'*-[(2R)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}-*N*-(4-methyl-thiazol-2-yl)-acetamide

colourless oil (18 mg, 28%).1H-NMR; $\delta(CD_3OD)$, 1H-NMR; $\delta(CD_3OD)$, 8.19 (0.3H, s, CHO), 7.80 (0.7H, s, CHO), 6.66 (1H, s, ArH), 3.8-3.1 (5H, m), 2.9-2.5 (1H, m, $NC\underline{H}Me_2$), 2.30 (3H, s, ArMe), 1.9-0.8 (17H, m). LRMS: +ve ion: 448 [M+23], 426 [M+1].

Example 10

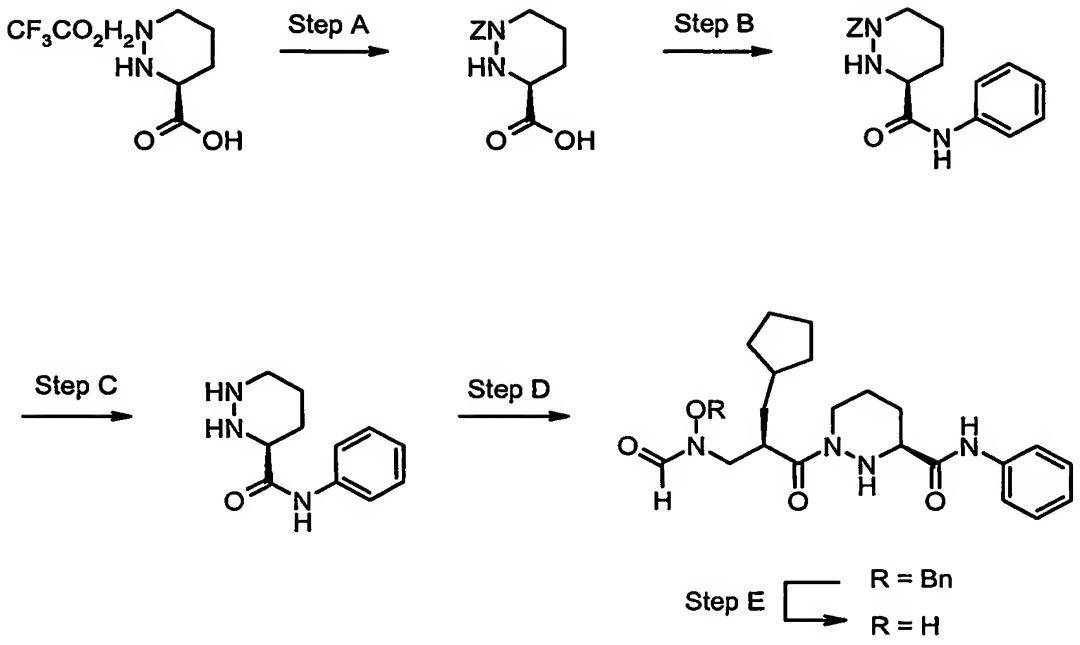
Prepared according to Reaction Scheme 1



N-Benzothiazol-2-yl-2-{*N'*-[(2R)-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}-acetamide

colourless oil (46 mg, 66%).1H-NMR; $\delta(CD_3OD)$, 1H-NMR; $\delta(CD_3OD)$, 8.19 (0.3H, s, CHO), 7.85 (1H, d, *J* 8, ArH), 7.80 (0.7H, s, CHO), 7.77 (1H, d, *J* 8, ArH), 7.43 (1H, t, *J* 8, ArH), 7.30 (1H, t, *J* 8, ArH), 3.9-3.1 (5H, m), 2.9-2.6 (1H, m, $NC\underline{H}Me_2$), 1.9-0.8 (17H, m). LRMS: +ve ion: 484 [M+23], 462 [M+1].

Example 11



Step A: $PhCH_2OCOCl$, 1M NaOH (aq), PhMe, 0 °C; Step B: EDAC.HCl, HOAt, aniline, DMF 0 °C to rt; Step C: H_2, 10% Pd/C, EtOH; Step D: 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid, EDAC.HCl, HOAt, 0 °C, 15 min, *then* piperazic acid amide, 0 °C to rt; Step E: H_2 (g), 10% Pd/C, EtOH, rt, 2 h.

Step A:

Tetrahydro-pyridazine-(1,3*S*)-dicarboxylic acid 1-benzyl ester

To a solution of (3*S*)-piperazic acid trifluoroacetic acid salt (129 mg, 0.53 mmol) in toluene/1M NaOH (1:1, 4 ml) at rt under argon was added benzyl chloroformate (114 µl, 0.79 mmol). The resulting solution was stirred for 1 h. After this time the mixture was diluted with water, washed with Et_2O (x3) and acidified to pH 5 with 1M HCl. The aqueous fraction was then extracted with EtOAc (x3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product as a white solid (125 mg, 89%). 1H-NMR; δ(CD_3OD), 7.5-7.2 (5H, m, Ph), 5.12 (2H, s, CH_2Ph), 4.0-3.8 (1H, m, NCH_AH_B), 3.6-3.5 (1H, m, $NCHCO_2$), 3.3-3.1 (1H, m, NCH_AH_B), 2.1-2.0

(1H, m), 1.8-1.5 (3H, m). LRMS: +ve ion: 287 [M+23], 265 [M+1].

Step B:

(3*S*)-Phenylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester

To a solution of tetrahydro-pyridazine-(1,3*S*)-dicarboxylic acid 1-benzyl ester (85 mg, 0.32 mmol) in DMF (2 ml) at 0°C under argon was added EDAC (74 mg, 0.39 mmol) and HOAt (66 mg, 0.48 mmol). The resulting mixture was stirred for 15 min before aniline (32 μL, 0.35 mmol) was added. The reaction was stirred for 15 min at 0°C and then warmed to rt where it was maintained for 16 h. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x2) and the combined organics washed with sat. $NaHCO_3$, sat. NaCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product as an oil. Purification by chromatography on silica eluting with 30% EtOAc/hexane gave the title compound as a colourless oil (83 mg, 76%).1H-NMR; δ(CD_3OD), 7.7-7.4 (2H, br s, ArH), 7.4-7.2 (7H, m, ArH), 7.07 (1H, t, J=7.5Hz, ArH), 5.20 (1H, d, J=5Hz, OCH_AH_BPh), 5.11 (1H, d, J=5Hz, OCH_AH_BPh), 3.82 (1H, dt, J=13 and 5Hz, NCH_AH_B), 3.69 (1H, t, J=5Hz, NCHCO), 3.4-3.2 (1H, m, NCH_AH_B), 2.3-2.1 (1H, m), 1.9-1.4 (3H, m). LRMS: +ve ion: 362 [M+23].

Step C:

Hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide

To a solution of the (3*S*)-phenylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (83 mg, 0.25 mmol) in EtOH at rt under argon was added 10% Pd/C (8 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give a colourless oil (49 mg, 98%) which was used immediately for the next step. LRMS: +ve ion: 228 [M+23], 206 [M+1].

Step D:

1-{(2*R*)-(Benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionyl}-hexahydro-

pyridazine-(3*S*)-carboxylic acid phenylamide

To a solution of 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid (44 mg, 0.15 mmol) in DMF (3 ml) at 0°C under argon was added EDAC (30 mg, 0.16 mmol) and HOAt (27 mg, 0.19 mmol). The resulting mixture was stirred for 15 min before a solution of hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide (27 mg, 0.13 mmol) in DMF (0.5 ml) was added. The reaction was stirred for 15 min at 0°C and then warmed to rt where it was maintained for 16 h. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x2) and the combined organics washed with sat. NaCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil. This oil was purified by chromatography on silica eluting with EtOAc to give the title compound as a colourless oil (18 mg, 25%).1H-NMR; δ($CDCl_3$), 9.56 (1H, br s, NH), 8.4-7.9 (1H, m, CHO), 7.8-7.0 (10H, m, ArH), 5.1-4.5 (3H, m), 4.0-3.0 (5H, m), 2.5-0.9 (15H, m). LRMS: +ve ion: 515 [M+23].

Step E:

1-[(2*R*)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide

To a solution of the 1-{(2*R*)-(benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionyl}-hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide (18 mg, 0.037 mmol) in EtOH (2 ml) at rt under argon was added 10% Pd/C (4 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give a colourless oil. This oil was purified by preparative HPLC to give the title compound as a colourless oil (8 mg, 50%). 1H-NMR; δ (CD_3OD), 8.26 (0.4H, s, CHO), 7.85 (0.6H, s, CHO), 7.7-7.5 (2H, m, ArH), 7.29 (2H, t, J=7.5Hz, ArH), 7.11 (1H, t, J=7.5Hz, ArH), 4.5-4.4 (1H, m, NCHCON), 4.2-3.2 (4H, m), 2.9-2.7 (1H, m), 2.2-0.8 (15H, m). LRMS: +ve ion: 425 [M+23], 403 [M+1].

Biological Example

Minimal Inhibitory concentrations (MIC) of inhibitors against clinical isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* obtained from the Public Health and Clinical Microbiology Laboratory, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QW, UK, were determined by a standard agar plate dilution method following recommendations in **British Society for Antimicrobial Chemotherapy Working Party**. 1991. "A guide to sensitivity testing British Society for Antimicrobial Chemotherapy, London, United Kingdom". Briefly Iso-Sensitest agar (pH 7.2: Oxoid, United Kingdom) was employed supplemented with 5% horse blood (Oxoid) and 20 μg of NAD (Sigma) per ml to support growth of fastidious bacteria. The inoculum used was approximately 10^4 colony forming units of each isolate contained in a volume of 1 μl. Plates were incubated 18 to 24 hr in air, or for fastidious bacteria an atmosphere enriched with 4-6% carbon dioxide at 35°C. The MIC was determined as the lowest concentration of an antimicrobial tested that inhibited growth of the inoculum, disregarding a single persisting colony or faint haze caused by the inoculation.

The compounds of the Examples were are antibacterially active in the above assays, The following table states the MIC ranges of the tested compounds against 3 strains of *S. pneumoniae*, 2 strains of *H. influenzae* and 1 strain of *M. catarrhalis.*

Example	S.pneumoniae μg/ml	H. influenzae μg/ml	M. catarrhalis μg/ml
2	4-16	8	0.5
3	16->32	0.5-1	0.5
4	1-2	32	0.5
5	1-4	>32	1
6	32->32	32	2
7	16-32	16-32	2
8	8-16	8->32	2
9	16-32	>32	2
10	1-4	>32	2